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Genetic variants IL18 -105G>A and -137G>C associated with susceptibility to migraine

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Introduction

Few studies have been conducted into neurogenic inflammation and neuroinflammation in respect of migraine. However, evidence suggests that the immune system may exert an influence over trigeminal activation and cortical spreading depression in individuals suffering from migraine. The interleukin (IL)-18 is a pro-inflammatory cytokine and increased plasma levels have been confirmed in individuals with migraine. However, as yet, the genetic variants of IL-18 have not been investigated in the context of migraine.

Objective

To investigate the association between genetic variants IL18 -105G>A (rs360717) and IL18 -137G>C (rs187238) and susceptibility to migraine and its clinical characteristics.

Subjects and Methods

Case control study comprising 307 participants, of whom 152 had a diagnosis of migraine and 155 were healthy controls, paired by sex, age, ethnicity and BMI. The clinical and demographic data were evaluated. The patients with migraine were interviewed using a structured form containing information about the type of migraine (with or without aura, episodic or chronic), age at onset of the disease, frequency of attacks, accompanying symptoms that triggered headaches. The patients also answered validated questionnaires to evaluate incapacity (Migraine Disability Assessment - MIDAS) and impact (Headache Impact Test - HIT-6) for migraine, the presence of allodynia (ASC-12), as well as symptoms of anxiety (State Anxiety Inventory - STAI 1 and 2), depression (Beck Depression Inventory) and a hyperacusis scale.

The genetic variants IL18 -105G>A (rs360717) and IL18 -137G>C (rs187238) were identified using polymerase chain reaction (PCR) and the fluorescence levels of PCR products were evaluated using a Step One thermocycler (Applied Biosystems). The analyses were conducted using the dominant, codominant, recessive and overdominant genetic models. Categorical data were evaluated via the chi-squared test or Fisher's exact test, and continuous data were evaluated using the Mann- Whitney test. Binary logistic regression was used to determine association when $p<0.1$ in the univariate analyses. A significant statistical difference was considered when $p<0.05$.

Results

The participants in the study were mostly female (76.8% and 81.6%, p = 0.23), young adults (median of 31 to 36 years, p = 0.30), Caucasian (76.8% and 82.2%, p = 0.21) and BMI with a median of 24.6 and 25.3 Kg/m2 in the control and migraine groups, respectively (p = 0.41).

55.6% of participants with migraine were classified as episodic while 44.4% were classified as chronic. Aura was present in 36.2%. Prophylactic medication was used in 44.7%, and 34.1% made excessive use of painkillers.

Alleles -105A and -137G were associated with higher susceptibility to migraine (OR = 1.53 with 95% CI 1.047-2.24; p = 0.028 and OR = 1.46 with 95% CI 1.00-2.14; p = 0.049, respectively). In the dominant model, the genotypes GA+AA of the IL-18 -105 variant were also associated with a higher chance of migraine (OR = 1.69 with 95% CI 1.05-2.73; p = 0.03).

The IL18 variants had no effect on the chronification of migraine, presence of aura, accompanying symptoms, prodrome, postdrome, triggers, age at onset, incapacity, impact, allodynia, hyperacusis, anxiety or depression.

Conclusions

The genetic variants of IL18 showed they exerted an effect on susceptibility to migraine; its alleles -105A and -137G, the major producers of cytokine, increased the chances of the disease by 53,0% and 46,0%, respectively. Results were in agreement with previous findings of higher IL-18 plasma levels in individuals with migraine. This was the first study to analyze the genetic variants of IL18 in migraine and results suggest that the IL18 variants do have an effect on susceptibility to migraine.

Keywords: Migraine, Cytokines, IL-18.